PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK2005/000199	22.03.2005	22.03.2004

International Patent Classification (IPC) or both national classification and IPC
C12N15/10, C12P21/02

Applicant
NUEVOLUTION A/S

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-178
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-178
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-178
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V.

1 Reference is made to the following documents:

D1 : WO 02/103008 A (NUEVOLUTION A/S (DK)); 27 December 2002 (2002-12-27)
D2 : WO 03/078625 A (NUEVOLUTION A/S (DK)); 25 September 2003 (2003-09-25)
D3 : WO 2004/013070 A (NUEVOLUTION A/S (DK)); 12 February 2004 (2004-02-12)
D4 : WO 2004/016767 A (HARVARD COLLEGE (US)); 26 February 2004 (2004-02-26)
D5 : WO 02/074929 A (HARVARD COLLEGE (US)) 26 September 2002 (2002-09-26)

2 Document D1, describes a method of preparing a library of complexes comprising templated molecules comprises contacting templates having a number of coding regions and a reactive group with building blocks, reacting a reactive group of a template and a reactive group of a building block to obtain a chemical connection, cleaving one or more of the linkers, and obtaining a templated molecule.

2.1 Document D2 describes a method of synthesizing a templated molecule comprising using at least one template comprising one or more codons, a first functional entity attached to a zipping domain comprising a 1st part of a molecule pair capable of reversible interaction with a 2nd part of the molecule pair, and one or more building blocks, each comprising an anti-codon, a further functional entity and a linker connecting the anti-codon and the functional entity.

2.2 Document D3 describes a method of synthesizing templated molecules with several functional groups comprising providing template having a sequence of coding elements, and building blocks, each having complementing element,

functional entity and linker separating the entity from the element, contacting each of the coding elements with a complementing element, and obtaining templated molecule having covalently linked functional groups.

2.3 Document D4 describes a method of performing nucleic acid-templated (NAT) synthesis, increasing the selectivity of NAT reactions, performing stereoselective NAT reactions, selecting for reaction products resulting from NAT synthesis and I identifying new chemical reactions based on NAT synthesis.

2.4 Document D5 describes a method of synthesizing one or more chemical compounds, involves providing one or more templates, which optionally have a reactive unit associated with them; and contacting one or more transfer units having an anti-codon and reactive unit with the one or more templates under conditions to allow for hybridization of the one or more anti-codons to template, and reaction of the reactive units.

2.5 Therefore, the subject-matter of claims 1, 9, 85 and 174 seems to be novel (Article 33(2) PCT).

3 D1, regarded as the closest state of the art, describes the formation of a single molecule by covalent linking at least two functional entities provided by separate templated molecules on a template molecule.

3.1 D1 differs from the subject-matter that describes a template directed synthesis, which lacks the essential technical feature of using a connector oligonucleotide guided synthetic method in which complementary identifier oligonucleotides of building blocks are capable of hybridizing to different connector oligonucleotide. In the light of D1, the problem of underlying application is the provision of a further synthetic method of bifunctional complexes. The solution as provided by the application is a **non template** directed synthesis method in which I) a plurality of building blocks at leat some of which comprise one or more chemical entities linked to an identifier oligonucleotide and ii) at least one connector oligonucleotide are iii) hybridised to each other, iv) ligating identifier oligonucleotides, v) separating the identifier

polynucleotide vi) reacting the chemical entities and vii) obtaining a bifunctional complex.

3.2 The combination of the technical features of the independent claim 1 is not rendered obvious by, the available prior art. Therefore, the present application does meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-178 provides an inventive step.

3.3 Claims 2-8, 10-84, 86-173 and 175-178 are dependent on claim 1, 9, 85 and 174 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

Re Item VI.

WO2004056994 (NUEVOLUTION) DK; 08 July 2004 (2004-07-08)
WO2004083427 (NUEVOLUTION) DK; 30 September 2004 (2004-09-30)

Re Item VIII.

1 Claims 1 and 85 lack clarity under Art. 6 PCT. The term **"connector oligonucleotide"** does not define the scope of the claim and is without technical significance and its vaguenesses makes it entirely open to individual interpretation. A template consisting of a single stranded nucleic acid sequence, e.g. presented in document D1, could also be regarded as a connector oligonucleotide. Reading claim 1 as: " A method for synthesising .. bifunctional complexes ... (ii) providing **one** connector oligonucleotide ... (iii) hybridising identifier oligonucleotides .. **to one** .. connector oligonucleotide ..etc. makes the subject-matter of claim 1 indistinguishable from the scope of document D1. The same is true for claim 85.

2 Claim 174 lacks clarity under Art. 6 PCT. Claim 174 describes a method for synthesising a plurality of different molecules, said method comprising a plurality of connector oligonucleotides each capable of hybridizing to at least 1 complementary connector olgonucleotide selected from the group of complementary connector olgonucleotide comprising at least one reactive group and/or 1 spacer group, hybridizing at least 2 complementary connector oligonucleotides and at least 2 connector oligonucleotides, wherein for each hybridisation complex at least 2 of said complementary connector oligonucleotides comprise at least 1 chemical entity comprising at least 1 reactive group.

This is contradictory, since In the absence of a so called "chemical entity" in the complementary connector oligonucleotides under claim 174e and 174f, said method does not work.

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